IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Ruggero FARIELLO *et al.*	Docket No:	373987–011 US (102895)
Serial No.:	10/559,982	Confirmation No.:	6583
Filed:	February 2, 2006 (§371)	Group Art Unit:	1617
For:	METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE	Examiner:	Sahar JAVANMARD

SECOND DECLARATION OF C. WARREN OLANOW UNDER 37 C.F.R. § 1.132

I, **C. WARREN OLANOW,** M.D., FRCPC, declare and state as follows:

1. This is the second Declaration that I am submitting in support of U.S. patent application no. 10/559,982. I have reviewed my first Declaration, and I reaffirm the statements made therein and incorporate them by reference into this second Declaration. The terms of my engagement have not changed, and I specifically reaffirm paragraphs 12 – 15 of my first Declaration. The views I am expressing in this second Declaration are entirely my own, and have not been influenced by any economic or professional interest in the outcome. The views expressed in this Declaration do not necessarily reflect the views of Mount Sinai School of Medicine, Mount Sinai Medical Center, or any other organization or entity for which I work, consult, or with which I am affiliated.

2. Since my first Declaration was filed, I have been appointed editor in chief of the journal *Movement Disorders*. In addition, two of the publications that had been listed on my *Curriculum Vitae* as having been "in press" have now been published,

- Olanow CW *et al.*, "The scientific and clinical basis for the treatment of Parkinson disease (2009)," *Neurology*. 72(21 Suppl 4):S1-136 (2009) (enclosed herewith as Exhibit A); and
- Olanow CW *et al.*, "A double-blind, delayed-start trial of rasagiline in Parkinson's disease," *New Engl. J. Med.* 361(13):1268-78 (2009),

and the following papers, not previously mentioned in my *CV*, have likewise been published or have been accepted for publication and are newly in press:

- Olanow CW, Prusiner SB, "Is Parkinson's disease a prion disorder?," *Proc. Natl. Acad. Sci. USA* 106(31):12571-2 (2009);
- Stockwell KA, *et al.*, "Continuous administration of rotigotine to MPTP-treated common marmosets enhances anti-parkinsonian activity and reduces dyskinesia induction," *Exp Neurol.* 219(2):533-42 (2009);
- Chu *et al.*, "Alterations in lysosomal and proteasomal markers in Parkinson's disease: relationship to alpha-synuclein inclusions," *Neurobiol Dis.* 35(3):385-98 (2009);
- Olanow and Kordower, "Modeling Parkinson's disease," *Ann Neurol.* 66(4):432-436 (Oct 2009) (enclosed herewith as Exhibit B); and
- Olanow CW, Kordower JH, Lang AE, Obeso JA, "Dopaminergic Transplantation for Parkinson's Disease: Current Status and Future Prospects," *Ann Neurol* (in press).

3. I have reviewed the final office action dated September 17, 2009 and the claims as examined. I understand that the Examiner has rejected all of these pending claims on the ground that:

> [i]t would have been obvious to one of ordinary skill in the art at the time of the invention to have combined safinamide, used to treat Parkinson's disease, as taught by Dostert, with a combination of L-dopa and a peripheral decarboxylase inhibitor, as taught by Birkmayer, for the same purpose. The motivation to combine these agents is provided by Chazot. Chazot teaches the coadministration of safinamide with that of L-dopa in the treatment of Parkinson's disease.[1]

4. For the reasons set out below, I disagree with the Examiner's reading of Chazot. In my opinion, Chazot cannot *possibly* motivate the use of safinamide as an "add-on" to clinically relevant doses of L-DOPA. And even if, *for sake of argument,* Chazot *were* to be credited with having motivated the adjunctive administration of safinamide with L-DOPA, *none*

[1] Final Office Action, p. 5.

of the experiments reviewed in Chazot would have led to a reasonable expectation that the oral administration of safinamide would successfully increase the therapeutic benefit of L-DOPA administered concurrently at a dose that alone has therapeutic effect.

Dostert, Birkmayer, and Chenard

5. As a preliminary matter, I do not have any major concerns with respect to the Examiner's characterization of the other references asserted in the rejection.

6. With respect to the Dostert reference, U.S. Pat. No. 5,236,957, I agree with the Examiner's general characterization: Dostert *does* teach the use of safinamide and its pharmacologically acceptable salts in the treatment of Parkinson's disease, but "Dostert does *not* teach the coadministration of L-dopa which is administered in an amount that alone has therapeutic effect."[2]

7. I have also reviewed the Birkmayer reference, U.S. Pat. No. 3,795,739, which the Examiner cites as teaching "a combination of L-dopa and a peripheral decarboxylase inhibitor." On first impression, this is a very curious characterization of the reference. The Birkmayer patent is clearly directed to the use of tryptophan and hydroxy-tryptophan to combat the cognitive and affective side effects of chronic L-DOPA treatment, not to the addition of a peripheral decarboxylase inhibitor to L-DOPA therapy.[3] Although there may initially have been some logic to the use of tryptophan, 35 years after the Birkmayer patent issued, tryptophan and hydroxytryptophan are not, and have never been, used in clinical practice in combination with L-DOPA. Nonetheless, regardless of whether Birkmayer is the reference best suited to support the Examiner's contention, I agree that that the use of peripheral decarboxylase inhibitors in combination with L-DOPA was well known and widely practiced in 2003.

8. The Examiner relies on Chenard, U.S. Pat. No. 6,258,827, as providing evidence that catechol-*O*-methyltransferase inhibitors, such as tolcapone or entacapone, were used in

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[2] Final Office Action, p. 4. The italic emphasis is mine.

[3] As an aside, Birkmayer and Hornykiewicz are generally credited with having (earlier) pioneered the use of levodopa for treatment of idiopathic Parkinson's disease.

combination with levodopa in 2003. I have reviewed Chenard, which is primarily directed to the use of NMDA antagonists with levodopa. As with Birkmayer, the exact nature of the Chenard disclosure seems to me to be of minor concern; for whatever the reference may or may not say, I can affirm that by 2003 the use of COMT inhibitors in combination with L-DOPA was well known and widely employed as a treatment for PD. I refer the Examiner to my 2001 review, Olanow *et al.*, "An algorithm (decision tree) for the management of Parkinson's disease (2001)," *Neurology* 56:1-88 (2001) (enclosed herewith as Exhibit C), for details about the standards of practice that were prevalent at the time.

Chazot

9. Turning, then, to the Chazot reference, "Safinamide: Newron Pharmaceuticals," *Current Opinion in Investigational Drugs* 2(6):809-813 (2001), I had noted in my first Declaration that Chazot "reviews the biochemical, pharmacological, and clinical properties of safinamide as had been reported publicly through early 2001." First Declaration, ¶ 39.

10. To rephrase that initial observation, *Chazot is a review* of safinamide's biochemical, pharmacological, and clinical properties -- it is not a primary report of peer-reviewed experimental results. Totaling only 5 pages, Chazot is best described as a *cursory* review.[4] Furthermore, only **3 paragraphs** in those 5 pages discuss safinamide's potential in the treatment of Parkinson's disease. Presenting no primary experimental data, and possessing no critical review or scholarly analysis of published literature, these 3 paragraphs **would not have motivated** a person of ordinary skill – an individual having a PhD in neuroscience or pharmacology, or a physician with an MD and special training in neurology – to take *any* experimental or clinical action *whatsoever* in furtherance of the idea that safinamide might have benefits in PD as an "add on" to therapeutic doses of levodopa. I cannot disagree more with the Examiner's contention that Chazot – in truth, 3 paragraphs in a perfunctory review article –

[4] I do not intend the term "cursory" as a term of subjective disparagement, but rather as an objective description of the limited scope and depth of the paper's content and scholarship. Contrast Chazot's 5 pages and 20 citations to the 136 pages and 1042 cited references of my own recently published review, Olanow *et al.*, "The scientific and clinical basis for the treatment of Parkinson disease (2009)," *Neurology* 72 (21 Suppl 4):S1-136 (2009) (enclosed herewith as Exhibit A).

would have motivated one of ordinary skill in the art of Parkinson's disease treatment to add safinamide to an underlying regimen of clinically-effective doses of L-DOPA.

11. *At the very most*, Chazot might have inclined a person of ordinary skill in the art to seek out the underlying primary references that are cited in the 3 paragraphs that are relevant to Parkinson's disease. Those 3 paragraphs are reproduced below (from page 810, right column):

> ***Parkinson's disease***
> As well as its activity for Na^+ and Ca^{2+} channels, safinamide also displays MAO-B inhibitory activity. Safinamide inhibited rat liver MAO-B and MAO-A with IC_{50} values of 100 nM and > 10,000 nM, respectively. Following administration of safinamide (5 mg/kg po) to rats, MAO-B inhibition was 79% after 1 h but only 13% after 24 h, suggesting a short-acting inhibitory action.
>
> Safinamide displayed clear activity in two animal models of PD. At a dose of 10 mg/kg, safinamide prolonged the rotational response to L-DOPA in 6-hydroxydopamine (6-OHDA)-lesioned rats. Furthermore, safinamide attenuated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced striatal dopamine depletion and loss of tyrosine hydroxylase-positive (dopaminergic) cells in the substantia nigra pars compacta. The underlying mechanism of action is likely to be blockade of MAO-B oxidation of MPTP to the neurotoxin, MPP^+ [345222]. However, safinamide (20 mg/kg) was also active in preventing dopaminergic neuron loss when given 4 h after MPTP, after the transformation to the neurotoxic metabolite MPP^+ by MAO-B has already occurred [403425].
>
> Recently, the effects of co-administration of L-DOPA with safinamide upon the motor activity of MPTP-treated mice were assessed. Safinamide injected 1 h before a subthreshold dose of L-DOPA (5 mg/kg) induced antiparkinsonian actions in MPTP-treated mice, including increases in locomotion and rearing behavior. A synergistic effect was suggested, as neither drug administered alone elicited beneficial effects on motor behavior of MPTP-treated mice [395700]. Elevation of dopamine in the neostriatum in toxic studies was reported in monkeys treated orally for 3 months [403425].

12. In this passage, Chazot mentions two studies in which safinamide was administered concurrently with L-DOPA in animal models.

13. Addressing the studies in reverse order of presentation, the last paragraph reproduced above summarizes a study, cited as reference [395700], in which "co-administration of L-DOPA with safinamide" in MPTP-treated mice was suggested to have "[a] synergistic effect." The cited reference is Fredriksson *et al.*, "Effects of co-administration of anticonvulsant and putative anti-convulsant agents and sub/suprathreshold doses of L-DOPA upon motor behavior of MPTP-treated mice," *J. Neural. Transm.* 106(9-10):889-909. This is the same Fredriksson article that I addressed at length in my first Declaration, and it should be sufficient here to quote my earlier-stated conclusions,

> Limited to experimental conditions in which L-Dopa was administered at doses that by themselves were clinically ineffective, **the Fredriksson experiments simply do not model or mimic any phenomenon that is relevant to treatment of Parkinson's patients**: physicians would never administer subtherapeutic doses of L-Dopa. Indeed, subtherapeutic doses of levodopa might worsen the parkinsonian status of a PD patient by acting on presynaptic dopamine receptors and thereby inhibiting dopamine synthesis and release. **The Fredriksson data simply do not speak to the relevant question, whether concurrent administration of safinamide would increase the therapeutic efficacy of therapeutically-effective doses of L-Dopa.**[5]
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> * * *
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> For all these reasons, it is my opinion that the animal model data in the Fredriksson reference would not have provided a person of ordinary skill in the art, in April 2003, with a reasonable expectation that the oral administration of safinamide would increase the therapeutic efficacy of ***clinically-relevant*** (that is, therapeutically effective) doses of L-Dopa being concurrently administered to patients with idiopathic Parkinson's disease.[6]

and to commend the Examiner's attention to the detailed reasoning in support of those conclusions that are set forth in the body of that earlier Declaration.

14. In the second paragraph of the passage reproduced above, Chazot summarizes a report in which "safinamide prolonged the rotational response to L-DOPA in 6-hydroxy-dopamine (6-OHDA)-lesioned rats." The report, cited as reference [345222], is an abstract by

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5 First Declaration, ¶ 31.

6 First Declaration, ¶ 37.

Ruggero Fariello[7] and his colleagues: Maj R *et al.*, "PNU-15177AE, a combined MAO-B and glutamate release inhibitor, is effective in animal models of Parkinson's disease," *Soc. Neurosci. Abstr.* 25 Part 2 Abs 640.16 (1999) ("Fariello abstract").

15. I addressed the Fariello abstract briefly in my first Declaration, in ¶¶ 21 and 40.

16. The Fariello abstract mentions two experiments. In the first, safinamide's ability to block the neurotoxic effects of MPTP was tested. Levodopa was not administered concurrently with safinamide in that experiment, and the experiment is not germane to the issues raised by the Examiner. In the second experiment, using

> the 6-OHDA rat model, animals were treated b.i.d. x 28 days with L-dopa (25 mg/kg plus benserazide 6.25 mg/kg; ip). In control rats the duration of the rotational response to L-dopa significantly decreased from day 1 to day 28. PNU-151774E (20 mg/kg, ip), administered on day 29, significantly reversed this effect.

17. This latter experiment directly parallels the "chronic" experiment reported in Fredriksson, substituting a 6-OHDA-lesioned rat for Fredriksson's MPTP-lesioned mice. As I explain in greater detail below, the 6-OHDA model shares the predictive infirmities of the MPTP model, and the Fariello experimental design shares the same predictive deficiencies as the Fredriksson experiment. As a consequence, Fariello adds nothing to the disclosure of Fredriksson, and certainly nothing that would dissuade me from the conclusion stated in my first Declaration: *even* were Chazot to be credited with having motivated the adjunctive administration of safinamide and L-DOPA in the treatment of Parkinson's disease, *none* of the experiments reviewed in Chazot would have led to a reasonable expectation that oral administration of safinamide would increase the therapeutic benefit of a clinically relevant dose of concurrently administered L-DOPA.

18. Like the MPTP-lesioned mice used by Fredriksson, Fariello's 6-OHDA lesioned rats have an acute toxin-induced lesion in the dopaminergic pathways affecting movement; as a consequence of the neuroanatomical lesion, the animals will rotate ipsilateral or contralateral to

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[7] Dr. Fariello is the first-named inventor of the present application.

the site of the lesion following the administration of amphetamine or apomorphine, respectively. Thus, the animals can be used to provide an indirect behavioral measure of an administered agent's dopaminergic activity and its effect on motor activity.

19. The predictive deficiencies of the rodent MPTP model, noted in my first declaration, apply equally to the 6-OHDA rodent model. Despite the apparent mimicry of certain pathologic features and symptoms of idiopathic Parkinson's disease, the MPTP ***and*** the 6-OHDA models are known to fall far short of recapitulating critical, components of idiopathic Parkinson's disease. The hallmark pathological feature of idiopathic Parkinson's disease is an intracellular proteinaceous inclusion known as the Lewy Body; in the MPTP and 6-OHDA models, Lewy bodies are not detected. Idiopathic Parkinson's disease is a chronic, progressive, neurodegenerative disorder; by contrast, in the standard MPTP and 6-OHDA models, the lesion are made acutely, and do not then progress. Idiopathic Parkinson's disease is known to include degeneration of non-dopaminergic extra-nigral neurons in the cerebral hemisphere, brain stem, spinal cord, and peripheral autonomic nervous system; whereas, in the MPTP and 6-OHDA models, the lesion is largely restricted to the substantia nigra and such extra-nigral damage is not detected. As it progresses, idiopathic Parkinson's disease causes autonomic dysfunction, sleep disturbances, mood disorders, psychosis and dementia, none of which are prominent features of animals that are acutely lesioned with MPTP. In particular, acute MPTP lesions in lower mammals, and even primates, is not known to reproduce the cognitive and affective impairments (such as depression and dementia) that are routinely seen as the disease progresses in human patients.[8]

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[8] *See*, First Declaration, ¶ 20.

20. Additionally, both MPTP and 6-OHDA lesions result in damage to approximately 95% of dopamine neurons, whereas clinical features in PD emerge after degeneration of only about 40-60% of dopamine neurons, and one does not see damage to more than 90% of neurons until the most advanced stage of the human disease. Finally, there are species differences particularly between rodents and humans. For example, dopaminergic agents routinely induce degeneration of retinal neurons in albino rats, while these changes have never been seen in PD patients. Similarly, dopaminergic agents are known to induce testicular adenomas in certain rodent species, but these have never been seen in PD patients. Conversely, dopaminergic agents are associated with an increased risk of melanoma in PD patients, while these have not been detected in animal models. For these and other reasons, drugs which have beneficial effects in these models do not necessarily have benefits in PD, and the side effect profile can be dramatically different.

21. As I noted in my first Declaration with respect to the MPTP model,

> Despite the apparent mimicry of certain pathologic features and symptoms of idiopathic Parkinson's disease, the MPTP mouse model has been shown over the years to be a poor model for predicting efficacy of potential therapeutic agents in human patients.[9] Some factors that contribute to the low predictive value include the high degree of species specificity in clinical responses to anti-parkinsonian agents, partly due to inter-species differences in brain bioavailability and dosing, and – as noted above – the lack of any relevant relationship of the acute MPTP lesion to the etiology and pathogenesis of cell death in PD. Positive results in the MPTP model do not assure positive results in the PD patients, and negative results in the MPTP mouse do not assure negative results in PD patients. There are many examples of agents that proved effective in the MPTP mouse, 6-OHDA rodent, or MPTP monkey, and later failed in PD patients. Indeed, in the history of modern Parkinson's disease therapy, far more of the agents that had first proved promising in these animal models subsequently failed in human clinical trials than ultimately obtained regulatory approval for use in human therapy.[10]

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9 Footnote in the original: "The same can be said of other rodent and primate models currently used in evaluating drugs for possible benefit in Parkinson's disease."

10 First Declaration, ¶ 21.

The same holds true for the 6-OHDA model. For example, the dopamine agonist, sumanirole, was shown to have enhanced effects in the 6-OHDA model compared to levodopa,[11] but was markedly inferior to levodopa in clinical trials in PD patients. Development of this drug was terminated by Pfizer based on the clinical trial results.

22. Even as a model of acute dopaminergic depletion, the 6-OHDA rat suffers deficiencies that make it less useful a prognosticator than the MPTP mouse model used by Fredriksson.

23. Like MPTP, 6-OHDA is dopamine analogue. It is taken up preferentially – but by no means exclusively – by catecholaminergic neurons, via the dopamine and norepinephrine reuptake transporters. Once internalized, 6-OHDA acts as an oxidative toxin. Although taken up preferentially by noradrenergic and dopaminergic neurons, 6-OHDA is far less cell type-selective than MPTP. It is also far more potent. Furthermore, unlike MPTP, 6-OHDA does not cross the blood-brain barrier; it must be injected stereotactically into the brain. As a consequence 6-OHDA's lower cell-type specificity, increased potency, and dependence on the situs of local injection, the lesion created by 6-OHDA is less specific, less focal, and less anatomically reproducible than that created by systemic administration of MPTP.

24. Typically, the 6-OHDA lesion is made unilaterally. The dopaminergic activity of an administered agent is then quantified by rotational movement, which is driven by the asymmetric response of the dopaminergic pathways. Although the 6-OHDA lesion allows compounds readily to be tested for dopaminergic activity, the observed behavioral outcome, either ipsilateral or contralateral rotation, is an even poorer proxy for the human symptoms of bradykinesia and tremor than are the activity and locomotor measures recorded in the MPTP model.

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[11] Some of the 6-OHDA data are published in McCall *et al.*, "Sumanirole, a highly dopamine D2-selective receptor agonist: in vitro and in vivo pharmacological characterization and efficacy in animal models of Parkinson's disease," *J. Pharmacol. Exper. Therapeutics*, 314(3):1228-1256 (2004) (enclosed herewith as Exhibit D).

25. The experimental design used by Fariello closely tracks that used by Fredriksson, a design that has two significant defects discussed at length in my first Declaration: (*i*) the 6-OHDA rat model, like the MPTP mouse model, is not accepted as a reliable model of the phenomenon of "wearing off"; and (*ii*) the intraperitoneal injection of safinamide cannot reliably predict its oral effects. First Declaration, ¶¶ 28, 32 – 35.

26. As I discussed at length in my first Declaration, the inadequacy of existing animal models of idiopathic Parkinson's disease is a pervasive and longstanding problem in the field, and by no means unique to the studies reviewed in Chazot. The limitations of current animal models of Parkinson's Disease are reviewed in my recent publication, Olanow and Kordower, "Modeling Parkinson's disease," *Ann Neurol.* 66(4):432-436 (Oct 2009) (enclosed herewith as Exhibit B). Quoting,

> [o]ne of the major obstacles [to the development of a neuroprotective agent for Parkinson's disease] is a model that reflects the etiopathogenesis of the disease and replicates its widespread pathology and progressive behavioral course in which to test putative neuroprotective interventions preclinically. Indeed, there are numerous examples of promising agents that have shown protective effects in the laboratory, but have failed to demonstrate benefits in clinical trials. While there are several critical factors that might contribute to this dilemma such as incorrect dosing and inadequacy of clinical endpoints, we believe the lack of a valid model is foremost.

Conclusion

27. For the reasons discussed above, it is my opinion that Chazot cannot *possibly* motivate the use of safinamide as an "add-on" to clinically relevant doses of L-DOPA. And even if, *for sake of argument,* Chazot *were* to be credited with having motivated the adjunctive administration of safinamide with L-DOPA, *none* of the experiments reviewed in Chazot would have led to a reasonable expectation that the oral administration of safinamide would successfully increase the therapeutic benefit of a dose of concurrently administered L-DOPA that alone has therapeutic effect.

28. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements and the like so made may jeopardize the validity or enforceability of U.S. Patent Application Serial No. 10/559,982, or any patent that issues therefrom.

11/12/09.
Date

C. Warren Olanow, M.D.